vera, adenocarcinoma, glioblastoma multiforma, leukemias, lymphomas, malignant melanomas, and epidermoid carcinomas.

5. (Amended) The method of claim 1, wherein the cancer are selected from the group consisting of acute myeloid leukemia, acute promyelocytic leukemia, acute lymphoblastic leukemia, and chronic myelogenous leukemia.

A4

31. (Amended) The method of claim 28, wherein the antimetabolic agent is selected from the group consisting of fluorouracil, floxuridine, methotrexate, leucovorin, hydroxyurea, thioguanine, mercaptopurine, cytarabine, pentostatin, fludarabine phosphate, cladribine, asparaginase, and gemcitabine.

A5

36. (Amended) The method of claim 35, wherein the immuno-modulating protein is selected from the group consisting of interleukin 2, interleukin 4, interleukin 12, interferon α, interferon β, interferon γ, erythropoetin, granulocyte-CSF, granulocyte, macrophage-CSF, bacillus Calmette-Guerin, levamisole, and octreotide.

REMARKS

This Amendment is in response to the Examiner's Office Action mailed June 17, 2002. Claims 2, 15 and 39-43 are canceled. Claims 1, 4, 5, 31 and 36 are amended. Claims 1, 3-14, and 16-38 are pending.

Reconsideration is respectfully requested in view of the above amendments and the following remarks. For the Examiner's convenience and reference, Applicants' remarks are presented in the order in which the corresponding issues were raised in the Office Action.

I. Objection to Claim 4

Claim 4 is objected to for misspelling the term "polycythemia" as "polycythermia". Applicants amend claim 4 to recite the correct term "polycythemia". Withdrawal of the objection is therefore respectfully requested.

II. Rejections under 35 U.S.C. §112, First Paragraph

The Examiner rejects claims 1, 2, 4, 6-28, 30 and 39-43 under 35 U.S.C. §112, First Paragraph for lack of enablement for a method for treating a disease associated with aberrant silencing of gene expression.

Applicants amend claim 1 to specify a method for treating cancer with a combination therapy. The combination therapy comprises administering to a patient suffering from cancer a DNA methylation inhibitor at a dose ranging from 1 to 50 mg/m^2 per day, in combination with a therapeutically effective amount of histone deacetylase inhibitor. The specification as filed provides ample exemplary support for such a treatment of various forms of cancer at page 29, lines 5-22. Specific examples of the DNA methylation inhibitor and the histone deacetylase inhibitor are provided at page 14, lines 19-24, and at pages 22-24, respectively. The specification as filed also discloses the method of administering the DNA methylation inhibitor and the histone deacetylase inhibitor by specifying the routes of administration and dosing regimens. See pages 36-38. In claim 1 as amended, the dose range of the DNA methylation inhibitor is specified to be from 1 to 50 mg/m^2 per day. Support for the claim language appears at page 36, lines 21-26.

Pursuant to MPEP 2164.04, Second Paragraph, the Examiner bears the burden of establishing a reasonable basis to question the enablement provided to for the claimed invention. *In re Wright*, 999 F.2d 1557, 1562 (Fed. Cir. 1993). The claimed invention is a combination therapy for treating cancer by co-administering a DNA methylation inhibitor (e.g., decitabine) at a dose of 1-50 mg/m^2 per day and a histone deacetylase inhibitor (e.g., phenylbutyrate or PB) in a therapeutically effective amount. The Examiner has not provided objective evidence to show that one of ordinary skill in the art would not know how to administer the two agents within the range of doses specified by claim 1.

In the rejection, the Examiner applied the eight factors enumerated in *in re Wands* to address the issue of whether undue experimentation is required to enable the full scope of the claims. *In re Wands*, 858 F.2d, 731, 737 (Fed. Cir. 1988). Particularly, the Examiner states that "the specification does not identify a specific disease or cancer being treated, the related gene being expressed in the combination therapy, and the effects of agents used, the invention is highly unpredictable regarding **the outcome of the treatment** without identifying the type and the disease state of the cancer" (emphasis added). Office Action, page 6, lines 16-19.

Applicants submit that the Examiner has confused the enablement requirement under 35 U.S.C. §112, First Paragraph with the utility requirement under 35 U.S.C. §101. The Examiner

asserts that the claims are not enabled because **the outcome of the treatment** is unpredictable. Such a consideration of safety and efficacy may be applied in addressing the utility issue under the patent law and in applying for the FDA approval. The Patent Office, however, has cautioned that there are substantial differences in the requirements for the FDA approval and those for satisfying the utility requirement for patentability:

> As a review matter [for the FDA approval], there must be a rational for believing that the compound could be effective. If the use reviewed by the FDA is not set forth in the specification, FDA review may not satisfy 35 U.S.C. §101. However, if the reviewed use is one set forth in the specification, Office personnel must be **extremely hesitant** to challenge utility (emphasis added).

MPEP 2107.03 V, first paragraph, lines 11-17. In the present invention what is claimed is a method to treat cancer by administering two agents to a patient, not a therapy with safety and efficacy profiles meeting the FDA's stringent requirements for approval. Thus, the Examiner's requirement of the outcome of the treatment is improperly applied in raising the enablement issue.

In the Specification Applicants have provided ample support for using the method to treat various forms of cancer. In challenging utility, the Examiner must bear the burden of proving that there is no sound rational for the asserted utility. The Examiner has not met such a burden.

In view of the failure of the Examiner to provide objective evidence that one of ordinary skill in the art would not know how to administer the two therapeutic agents in claim 1, based on the ample exemplary support in the specification as originally filed Applicants submit that independent claim 1 is sufficiently enabled throughout its scope. Withdrawal of the rejection under 35 U.S.C. §112, First Paragraph is respectfully requested.

III. Rejections under 35 U.S.C. §112, Second Paragraph

a) Omission of steps

The Examiner rejects claims 1, 2, 4, 6-28 and 30 under 35 U.S.C. §112, Second Paragraph as being indefinite for omitting the steps of administration and the outcome of the treatment. Claim 1 as amended specifies the step of administration by reciting the doses of the two agents used in the combination therapy.

b) "Disease associated with aberrant silencing of genes"

The Examiner also rejects claims 1, 2, 4, 6-28, 30 and 39-43 under 35 U.S.C. §112, Second Paragraph as being indefinite for using the term "a disease associated aberrant silencing of gene expression". Applicants amend claim 1 to specify the disease to be "cancer".

c) Non-elected inventions

The Examiner also rejects claims 2, 4, 28 under 35 U.S.C. §112, Second Paragraph as being indefinite **because the claim contains non-elected inventions**. The Examiner's rational in rejection is in error because claims do not become indefinite simply because they contain non-elected inventions. To satisfy the Examiner's Restriction Requirement Applicants may elect certain species not others contained in the same claim. The species not elected are not automatically rendered indefinite absent the Examiner's showing of evidence proving that the non-elected species are not sufficiently definite to one of ordinary skill in the art.

d) "Cytidine analog"

The Examiner also rejects claim 6 under 35 U.S.C. §112, Second Paragraph as being indefinite for the use of the term "cytidine analog". Cytidine is a chemical with a distinct structure, and its analog should be one with substantially similar chemical structures such as 5-azacytidine and 5-aza-2'-deoxycytidine disclosed in the specification. Applicants submit that one of ordinary skill in the art, in view of the specification, would be able to ascertain what a cytidine analog is based on the understanding of the chemical structure of cytidine.

e) "FR901228" and "MS-27-275"

The Examiner also rejects claims 10, 11, 41 and 42 under 35 U.S.C. §112, Second Paragraph as being indefinite for containing the terms "FR901228" or "MS-27-275". MS-27-275 is described in the specification at page 23, lines 24-25 and its chemical structure shown in Figure 2 under "III Butyamides". MS-27-275 is known to one of ordinary skill in the art as shown in the reference Saito et al. (1990) Proc. Natl. Acad. Sci. USA. 96:4592-4597 cited in the specification at page 23, lines 24-25. FR901228 is also called depsipeptide and described in the specification at page 23, lines 22-23. FR901228 is well known to one of ordinary skill in the art as evidenced in the abstracts of two references contained in Exhibit A Applicants submit herewith: Piekarz et

al. (2001) Blood 98:2865-2868; and Kitazono et al. (2002) Blood 99:2248-2251. In view of the disclosure in the specification and references provided, Applicants submit that the terms "FR901228" and "MS-27-275" are sufficiently definite to one of ordinary skill in the art.

Further, as stated in MPEP 2173.01, a fundamental principle contained in 35 U.S.C. 112, second paragraph is that applicants are their own lexicographers. They can define in the claims what they regard as their invention essentially in whatever terms they choose so long as the terms are not used in ways that are contrary to accepted meanings in the art. As long as one of ordinary skill in the art understands what the claim means in view of the claim language and specification, it is not necessary to describe the name of a compound by reciting its formal chemical nomenclature as required by the Examiner. For example, although the formal chemical name of decitabine is 5-aza-2'-deoxycytidine, a claim can recite "decitabine" in lieu of "5-aza-2'-deoxycytidine".

f) "One or more"

The Examiner also rejects claim 28 under 35 U.S.C. §112, Second Paragraph as being indefinite for the use of the term "one or more". Specifically, the Examiner asserts that the term "one or more' renders the claim indefinite because it is not clear how many antineoplastic agents are administered as to "one or more". Applicants submit that the term "one or more antineoplastic agents" has a very clear and unambiguous meaning. It simply means that one, two, or more antineoplastic agents ($\geq$ 1 agent) could be administered to the patient in combination with the DNA methylation inhibitor and the histone deacetylase inhibitor. Applicants fail to see how that term renders the claim indefinite.

Given the teachings in the specification and in the existing art and the level of skill in the art, Applicants believe that the pending claims are sufficiently definite and well understood by one of ordinary skill in the art. Withdrawal of the ground of rejection under 35 U.S.C. §112, Second Paragraph is therefore respectfully requested.

IV. Rejections under 35 U.S.C. §102(b) and §103(a)

a) Rejection under 35 U.S.C. §102(b) and §103(a) in view of Guan et al.

The Examiner rejects claims 1, 2, 4, 6-8 and 12 under 35 U.S.C. §102(b) as being anticipated by or, in the alternative, under 35 U.S.C. §103(a) as being obvious over Guan et al.

(Cancer Res. (2000) 60:749-755). Specifically, the Examiner states that Guan et al. teach the use of a histone deacetalase inhibitor such as trichostatin A, or a combination of tributyrin (a prodrug of butyrate) and decitabine to up-regulate the expressio of Drg-1 (a putative metastatic suppressor gene in human colon cancer) in metastatic colon cancer cells.

Independent claim 1 as amended specifies a method for treating a cancer patient with a combination therapy. The combination therapy comprises administering to a patient suffering from cancer a DNA methylation inhibitor (e.g., decitabine) at a dose ranging from 1 to 50 mg/m^2, in combination with a therapeutically effective amount of histone deacetylase inhibitor (e.g., phenylbutyrate or PB).

In contrast, Guan et al. discloses a study of Drg-1 gene function in cell culture and nude mice. This study was focused on elucidating the role Drg-1 gene plays in metastasis of colon cancer, as evidenced by the extensive in vitro and in vivo studies in order to determine if overexpression of Drg-1 would suppress liver metastasis. For example, Guan et al. implanted nude mice with colon cancer cells stably transfected with a vector pcDNA3.1 containing Drg-1 cDNA. Page 750, left column, under "Generation of Drg-1 Stable Transfectants". Agents such as decitabine, trichostatin A, and tributyrin were merely used to validate the role Drg-1 gene plays in metastasis of colon cancer. Page 752, right column, lines 5-14. Nowhere in this reference could be found a teaching or suggestion of the claimed method for treating cancer patient with a combination of a DNA methylation inhibitor and a histone deacetylase inhibitor following the specific regimen recited in claim 1.

In view of the failure of Guan et al. to teach or suggest the specific therapeutic regimen as claimed, the claimed invention is not anticipated by the cited reference under 35 U.S.C. §102(b). Since the cited reference fails to teach or suggest all of the claim elements, a prima facie case of obviousness has not been established under 35 U.S.C. §103(a). Withdrawal of the rejection under these grounds is therefore respectfully requested.

b) Rejection under 35 U.S.C. §103(a) over Guan et al. in view of Cameron et al.

The Examiner rejects 9 under 35 U.S.C. §103(a) as being obvious over Guan et al. and Cameron et al. (Nature Genetics (1999) 21: 103-107).

As discussed in detail above, Guan et al. focused on studying the role of Drg-1 gene in suppression of colon cancer metastasis in cell culture and in nude mice. Similar to Guan et al., Cameron studied the effects of decitabine and trichostatin T in reactivating expression of genes

such as MLH1 and p16 in vitro. See "Abstract". Neither Guan et al. nor Cameron, alone or in combination, teaches or suggests treating a cancer patient following the specific regimen recited in claim 1.

Since the cited references fail to teach or suggest all of the claim elements, a prima facie case of obviousness has not been established under 35 U.S.C. §103(a). Withdrawal of the rejection under this ground is therefore respectfully requested.

c) Rejection under 35 U.S.C. §103(a) over Guan et al. in view of Boyd et al.

The Examiner rejects 9 under 35 U.S.C. §103(a) as being obvious over Guan et al. and Boyd et al. (U.S. Patent No: 5,283,383).

As discussed in detail above, Guan et al. focused on studying the role of Drg-1 gene in suppression of colon cancer metastasis in cell culture and in nude mice. Guan et al. fails to teach or suggest the claimed combination therapy for treating a cancer patient.

The secondary reference, Boyd et al., fails to supply the requisite elements missing in Guan et al. As acknowledged by the Examiner, Boyd et al. merely teaches a method of treating cancer with a combination of 6(R)-bromo-3(S)-bromomethyl-7-methyl-2,3,7-trichloro-1-octene and doxorubicin. Nowhere in this reference could be found a teaching or suggestion of the claimed method of treating cancer patient following the specific regimen recited in claim 1.

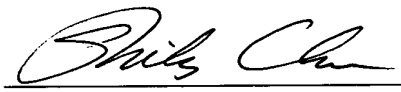
In view of the failure of the cited references to teach or suggest all of the claim elements, a prima facie case of obviousness has not been established under 35 U.S.C. §103(a). Withdrawal of the rejection under this ground is therefore respectfully requested.

CONCLUSION

Applicants earnestly believe that they are entitled to a letters patent, and respectfully solicit the Examiner to expedite prosecution of this patent application to issuance. Should the Examiner have any questions, Examiner is encouraged to telephone the undersigned.

Respectfully submitted,

Date: September 17, 2002

By: 

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Specification:

Paragraph beginning at line 14 of page 7 has been amended as follows:

--Cancer vaccines are a group of agents that induce the body's specific immune response to tumors. Most of cancer vaccines under research and development and clinical trials are tumor-associated antigens (TAAs). TAA are structures (i.e. proteins, enzymes or carbohydrates) which are present on tumor cells and relatively absent or diminished on normal cells. By virtue of being fairly unique to the tumor cell, TAAs provide targets for the immune system to recognize and cause their destruction. [Example] Examples of TAAs include gangliosides (GM2), prostate specific antigen (PSA), 36. (Amended) The method of claim 35, wherein the immuno-modulating protein is selected from the group consisting of interleukin 2, interleukin 4, interleukin 12, interferon α, interferon β, interferon γ, erythropoietin, granulocyte-CSF, granulocyte, macrophage-CSF, bacillus Calmette-Guerin, levamisole, and octreotide. -fetoprotein (AFP), carcinoembryonic antigen (CEA) (produced by colon cancers and other adenocarcinomas, e.g. breast, lung, gastric, and pancreas cancer[s]), melanoma associated antigens (MART-1, gp100, MAGE 1,3 tyrosinase), papillomavirus E6 and E7 fragments, whole cells or portions/lysates of antologous tumor cells and allogeneic tumor cells.--

In the Claims:

Claims 2, 15 and 39-43 have been canceled.

Claims 1, 4, 5, 31 and 36 have been amended as follows:

1. (Amended) A method for treating cancer with a combination therapy [a disease associated with aberrant silencing of gene expression], comprising:

administering to a patient suffering from [the disease] cancer [a therapeutically effective amount of] a DNA methylation inhibitor at a dose ranging from 1 to 50 mg/m^2 per day, in combination with [an] a therapeutically effective amount of histone deacetylase inhibitor.

4. (Amended) The method according to claim [2] 1, wherein the cancer is selected from the group consisting of breast cancer, skin cancer, bone cancer, prostate cancer, liver cancer, lung cancer, brain cancer, cancer of the larynx, gallbladder, pancreas, rectum, parathyroid, thyroid, adrenal, neural tissue, head and neck, colon, stomach, bronchi, kidneys, basal cell carcinoma, squamous cell carcinoma of both ulcerating and papillary type, metastatic skin carcinoma, osteo sarcoma, Ewing's sarcoma, veticulum cell sarcoma, myeloma, giant cell tumor, small-cell lung tumor, gallstones, islet cell tumor, primary brain tumor, acute and chronic lymphocytic and granulocytic tumors, hairy-cell tumor, adenoma, hyperplasia, medullary carcinoma, pheochromocytoma, mucosal neuronms, intestinal ganglloneuromas, hyperplastic corneal nerve tumor, marfanoid habitus tumor, Wilm's tumor, seminoma, ovarian tumor, leiomyomater tumor, cervical dysplasia and in situ carcinoma, neuroblastoma, retinoblastoma, soft tissue sarcoma, malignant carcinoid, topical skin lesion, mycosis fungoide, rhabdomyosarcoma, Kaposi's sarcoma, osteogenic and other sarcoma, malignant hypercalcemia, renal cell tumor, [polycythermia] polycythemia vera, adenocarcinoma, glioblastoma multiforma, leukemias, lymphomas, malignant melanomas, and epidermoid carcinomas.

5. (Amended) The method of claim [2] 1, wherein the [hematological disorders] cancer are selected from the group consisting of acute myeloid leukemia, acute promyelocytic leukemia, acute lymphoblastic leukemia, and chronic myelogenous leukemia[, the myelodysplastic syndromes, and sickle cell anemia].

31. (Amended) The method of claim 28, wherein the [the ntimetabolic] antimetabolic agent is selected from the group consisting of fluorouracil, floxuridine, methotrexate, leucovorin, hydroxyurea, thioguanine, mercaptopurine, cytarabine, pentostatin, fludarabine phosphate, cladribine, asparaginase, and gemcitabine.

36. (Amended) The method of claim 35, wherein the immuno-modulating protein is selected from the group consisting of interleukin 2, interleukin 4, interleukin 12, interferon α, interferon β, interferon γ, erythropoietin, granulocyte-CSF, granulocyte, macrophage-CSF, bacillus Calmette-Guerin, levamisole, and octreotide.